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09/912,020	07/23/2001	Judith Zyskind	FLITRA.001DV1	4741

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EXAMINER

ANGELL, JON E

ART UNIT	PAPER NUMBER
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1635

17

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/912,020

Applicant(s)

ZYSKIND ET AL.

Examiner

J. Eric Angell

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 May 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 July 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. This Action is in response to the communication filed on 5/20/03, as Paper No. 16. The amendment has been entered. Claims 1, 4 and 11 have been amended. Claims 1-20 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

The claims have been restricted to two specific antisense molecules (SEQ ID NO. 459 and SEQ ID NO. 460, which substantially overlap), for the reasons of record. Applicants elected the antisense molecules of SEQ ID NO. 459 and SEQ ID NO. 460 with traverse, in the paper filed 11/6/02.

Specification

The objection to the specification has been withdrawn as the specification has been amended to remove the embedded hyperlinks.

Claim Rejections - 35 USC § 112, second paragraph

3. The rejections of claims under 35 U.S.C. 112, second paragraph, as being indefinite have been withdrawn in view of the claim amendments.

Claim Rejections - 35 USC § 112, first paragraph

1. Claims 1-4, 8-12 and 15-20 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record.

Response to Arguments

2. Applicant's arguments filed 5/20/03 have been fully considered but they are not fully persuasive. Applicants' arguments are only persuasive to the extent that the specification has adequately described antisense molecules that are specific for the nucleic acid sequence that encodes the polypeptide sequence of SEQ ID NO. 325 (i.e. molecules antisense to SEQ ID NO. 165). However, the instant claims are very broad and encompass non-antisense molecules as well as antisense molecules that are antisense to a "gene corresponding to SEQ ID NO. 165" (see claims 11 and 12). The specification does not adequately describe the non-antisense molecules encompassed by the claims or the antisense molecules targeted to "genes corresponding to SEQ ID NO. 165".

Applicants argue that two antisense molecules that inhibit the proliferation of four different organisms have been described. Applicants note that they were the first to determine the polypeptide sequence of SEQ ID No. 325 (encoded by SEQ ID NO. 165) is involved in cellular proliferation and assert that the identification of the biological role of a protein coupled with a demonstration that inhibiting the activity or reducing the amount of the polypeptide or nucleic acid encoding the polypeptide inhibits cellular proliferation is sufficient to support the claims. Applicants also point to a number of different patents that allegedly have been issued

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wherein the patents claim a generic class of compounds that achieve a particular biological activity. Applicants also contend that the specification disclose particular antisense compounds complimentary to the gene encoding SEQ ID NO. 325 which inhibit cellular proliferation and have identified methods of identifying additional antisense nucleic acids having the same function (e.g., Example 1). Applicants also argue that they have identified methods for identifying triplex forming molecules as well as PNAs that have the desired function. Furthermore, Applicants contend that methods of screening combinatorial chemical and/or natural product libraries for small molecules having the desired function. With respect to the description of antisense molecules specific for the nucleic acid encoding SEQ ID NO. 325, Applicants refer to Example 15 of the written description guidelines and compare the instant disclosure with Example 15 (see p. 8-12 of the response).

In response, it is acknowledged that the instant specification is analogous to Example 15 of the Written Description Guidelines, so far as the claims are drawn to antisense molecules that are targeted to SEQ ID NO. 165 and inhibit the expression of the polypeptide encoded by SEQ ID NO. 165 (i.e. inhibit the expression of SEQ ID NO. 325). However, as previously mentioned (and acknowledged by the Applicants) the claims are not limited to antisense molecules that are targeted to SEQ ID NO. 165 and inhibit expression of the its encoded polypeptide and encompass molecules which have yet to be identified. With respect to the description of non-antisense molecules, it is acknowledged that the specification has indicated methods of screening libraries for inhibitors as well as methods for designing other inhibitory molecules (e.g., PNAs, triplex forming molecules). Here the specification has not identified the structures of any of the small molecules that have the desired inhibitory activity, nor is there any guidance indicating any

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particular structure that would be common to all of the small molecules that would confer the inhibitory function to the molecules. Therefore, although a method of possibly identifying small molecule inhibitors (and the like) is disclosed, a representative number of these molecules have not been disclosed and one of skill in the art would not be able to readily recognize any such small molecule inhibitor. Therefore, the written description requirement with respect to small molecule inhibitors has not been met. With respect to the claims as they encompass non-antisense inhibitory molecules based on the sequence encoding SEQ ID NO. 325 (i.e. PNAs, triplex-forming molecules), it is acknowledged that the specification has given some general guidance on designing these molecules and has disclosed how to test these molecules. However, the specification has not adequately described a sufficient number of these compounds to meet the written description requirement because the specification has not explicitly described any specific PNA/triplex-forming molecule that has the inhibitory function. The guidance provided merely is an invitation to perform further experimentation in to identify the inhibitors.

Therefore, the written description requirement has not been met in this case.

With respect to the description of antisense molecules targeted to genes corresponding to SEQ ID NO. 165, it is respectfully pointed out that the claims encompass proliferation-inhibitory antisense molecules targeted to homologues of SEQ ID NO. 165. It is well known to persons skilled in the art that sequences which appear to be homologous do not always have the same function (for instance, it is well known that sickle cell anemia is caused by a single nucleotide change in the gene encoding hemoglobin); therefore, the claims encompass antisense molecules to genes which may not be associated with cellular proliferation. Therefore, in order to be able to make antisense molecules targeted to homologues of SEQ ID NO. 165 that actually inhibit

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cellular proliferation, experimentation must first be performed in order to determine if the homologue is a gene involved in cellular proliferation. The specification has not described the structural characteristics that would be common to all homologues, therefore, one of skill in the art would not readily recognize which homologues would be involved in cell proliferation and which ones would not. Without a clear indication of the homologues of SEQ ID NO. 165 involved in proliferation, one of skill in the art would not readily recognize the antisense molecules would inhibit proliferation. Therefore, the specification fails to adequately describe the proliferation-inhibitory antisense molecules targeted to SEQ ID NO. 165 homologues.

Regarding Applicants argument that other patents have been issued wherein a broad genus of inhibitors have been claimed, it is pointed out that each application is examined on its own merits and the circumstances of other applications/patents are not considered in the examination of the instant application.

In summary, although the Applicants arguments with respect to inhibitory antisense molecules targeted specifically to SEQ ID NO. 165 are persuasive, the claims are very broad and encompass molecules that have not been adequately described in the specification, such as small molecules, PNAs, triplex-forming molecules, antisense molecules targeted to sequences that are homologues of SEQ ID NO. 165, and other non-antisense molecules. Therefore, the rejection of the claims 1-4, 8-12 and 15-20 is appropriate and the rejection is not withdrawn.

3. Claims 1-20 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

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A method for inhibiting the proliferation of *E. coli*, *S. Typhimurium*, *E. cloacae* or *K. pneumoniae* cells in vitro (i.e., not in a subject) by administering an antisense nucleic acid sequence selected from the group consisting of SEQ ID NO: 459 and 460 to said cells wherein said administration of said antisense nucleic acid molecule results in inhibiting the proliferation of said cells; does not reasonably provide enablement for the full breadth of the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record, which are summarized below.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The instant claims are drawn to a method for inhibiting cellular proliferation by inhibiting the activity or reducing the level of the amino acid sequence of SEQ ID NO: 325. The specification indicates that the SEQ ID NO: 325 is a gene involved in proliferation of *E. coli* and indicates that specific antisense molecules can be used to inhibit cellular proliferation of certain

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bacterial cells; it is asserted that the antisense molecules can act as antibiotics. Therefore one aspect of the invention is antisense therapy.

The breadth of the claims

The broadest claims are very broad and encompass inhibiting cellular proliferation of any cell by administering any compound that inhibits the activity or reduces the level of the amino acid sequence of SEQ ID NO: 325. It is noted that the specification contemplates using the antisense molecules as antibiotics. Therefore the claims encompass inhibiting the proliferation of bacterial cells that are in an animal (i.e. in vivo) as well as inhibiting the proliferation of bacterial cells that are outside an animal (i.e. in vitro). As mentioned in the written description rejection above, the claims also encompass administering any compound comprising the antisense molecules and functional (i.e. proliferation-inhibiting fragments of the antisense molecules).

The unpredictability of the art and the state of the prior art

As mentioned above the claims encompass using the antisense molecules as antibiotics to inhibit the proliferation of bacterial cells in an animal. However, the relevant art recognizes several problems with using antisense molecules for treatment in animals/humans. First, it is clear that ordinary, unmodified DNA and RNA oligonucleotides are rapidly degraded by enzymes in the body and that the resulting nucleoside monophosphates are toxic (e.g. see Dove Nat. Biotech. 2002; 20:121-124; Lebedeva et al. Ann. Rev. Pharmacol. Toxicol. 2001; 41:403-419; and Branch TIBS 1998; 23:45-50). Furthermore, the art also recognizes that antisense molecules can have non-specific effects. Specifically, Branch teaches,

“[T]he antisense field has been turned on its head by the discovery of ‘non-antisense’ effects, which occur when a nucleic acid drug acts on some molecule other than its intended target—often through entirely unexpected mechanism. Non-antisense effects are not necessarily bad. Indeed, some may prove to be a boon to the pharmaceutical

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industry because they offer an added source of potency. However, their unpredictability confounds research applications of nucleic acid reagents.” (See p. 45 middle column).

Branch also indicates that longer antisense molecules are not necessarily better and can have negative effects. Specifically, Branch teaches that increasing the length of the antisense molecule beyond the minimum is likely to decrease its specificity by stabilizing binding to mismatched sequences (see p. 47 last column). Figure 1 on page 48 of Branch indicates that a long antisense molecule may bind to the target RNA well as mismatched “by-stander” RNA and both RNAs get destroyed. Branch also teaches, “Because non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs. These effects must be explored on a case-by-case basis.” (See p. 50, first column).

The “by-stander” effect also has to be considered when using the antisense molecules to inhibit the proliferation of other bacterial species. For example, it would be readily apparent to one of ordinary skill in the art there would likely be variations of the same gene in different species of bacteria. Therefore, it is possible that there could be mismatch binding of the antisense molecules to other “by-stander” RNAs. Therefore one of ordinary skill in the art could not predictably use the antisense molecules of SEQ ID NO: 459 or 460 to inhibit the proliferation of any bacterial cell without performing additional experimentation.

Working Examples and Guidance in the Specification

The specification indicates that the specific antisense molecules of SEQ ID NO: 459 and 460 were given to E. coli, S. Typhimurium, E. cloacae or K. pneumoniae cells in vitro (i.e., not in a living subject) and the results indicate that the treatment inhibited proliferation of these cells (e.g., see Mol No. EcXA033 in the Table on p. 95, as well as the figures and Examples 1-3, p. 31-37).

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However, the specification does not indicate that the antisense molecules were given to any animal having a bacterial infection. The specification does not disclose that the antisense molecules were given to any other bacterial cells other than those already mentioned, nor does the specification indicate that any fragments of the antisense molecules have been tested or that any molecules comprising the antisense molecules of SEQ ID NO: 459 and 460 have been administered.

Quantity of Experimentation

Considering the breadth of the claims and the limited amount of working examples/guidance in the specification; additional experimentation would be required in order for one of ordinary skill in the art to: 1) identify all of the compounds encompassed by the claims (see written description rejection, above); 2) show that the compounds have an antiproliferative effect on all of the cells encompassed by the claims in vitro; 3) test the efficacy of the compounds on animals that were infected with the bacterial cells.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the unpredictability of antisense therapy recognized in the art—especially the non-specific effects of antisense therapy, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

4. Applicant's arguments filed 5/20/03 (see pages 13-17) have been fully considered but they are not persuasive.

5. The claims have been rejected as not being enabled for the full scope encompassed by the claims. As previously mentioned the claims are very broad. For instance the claims encompass inhibiting the growth of any cell by administering a compound which inhibits the activity or expression of a polypeptide encoded by SEQ ID NO. 165 or a homologue of SEQ ID NO. 165. The claims encompass inhibiting the proliferation of these cells in a subject (i.e. in vivo) as well as in culture (in vitro). The claims are not fully enabled for the reasons of record.

6. Applicants contend that the specification provides ample guidance to enable one of skill in the art to practice the claimed invention over the entire scope encompassed by the claims without undue experimentation. Applicants argue that extensive guidance is provided for identifying the inhibitory compounds, including screening libraries to identify the inhibitors. Applicants also refer to Examples 8 and 9 of the specification which describe methods of identifying and testing inhibitory compounds. Applicants argue that they have provided enough guidance for one of skill in the art to inhibit the proliferation of any organism that possesses the waaE gene. Regarding the lack of enablement for inhibiting cell proliferation in vivo, applicants argue that the specification has described a number of ways to stabilize antisense molecules for use in vivo.

7. In response, Applicants' arguments have been fully considered, but they are not persuasive. Regarding the inhibiting cell proliferation wherein the cells are in a subject it is reiterated that there are a number of problems associated with using antisense molecules as

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therapeutic compounds for treating subjects including: degradation of the molecule, delivery of the molecule to the target cell, and possible "by-stander"/non-antisense effects of the molecules. Applicants have argued that they have described methods of modifying the antisense molecules to increase their half-life; however, the Applicants have not overcome the problems associated with non-antisense effects. Furthermore, considering the art recognizes that non-antisense effects cannot be overcome by routine experimentation, an undue amount of additional experimentation would be required in order to be able to inhibit cell growth in vivo.

8. Regarding the method with respect to inhibiting the proliferation of any cell. It is respectfully pointed out that the only working examples provided indicate that antisense molecules specific for SEQ ID NO 165 (specifically antisense molecules SEQ ID NO 459 and 460) can inhibit the growth of four specific types of cells: *E. coli*, *S. Typhimurium*, *E. cloacae* or *K. pneumoniae* (and only in vitro). One considering the difficulty of designing functional antisense molecules recognized in the art and previously mentioned (see teachings of Branch) it would not be predictable that the antisense molecules would work in every cell type. In order for the molecules to inhibit growth on the target cells the molecules would have to specifically bind to their target sequences which must be involved in cell proliferation. As previously mentioned, the claims encompass targeting homologues of SEQ ID NO. 165. It is not predictable that every homologue of SEQ ID NO. 165 would have the same function. Therefore, without evidence to the contrary, it is unpredictable that the proliferation of any cell could be inhibited using the claimed invention. In the instant case, the only evidence presented is that the specific antisense molecules can inhibit the proliferation of *E. coli*, *S. Typhimurium*, *E. cloacae* and *K. pneumoniae*, wherein the cells are in vitro.

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9. Regarding the rejection as it applies to using any inhibitor of waaE activity or expression, it is noted that the specification has only adequately described the inhibitors that are antisense inhibitors of waaE expression, as mentioned above. Without an adequate description of a sufficient number of species encompassed by the claims, one of ordinary skill in the art would not know to make and use the invention without performing additional experimentation.

10. Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn.

11. It is noted that the claims are enabled for inhibiting the proliferation of E. coli, S. Typhimurium, E. cloacae and K. pneumoniae in vitro by administering antisense molecules that are targeted to SEQ ID NO. 165 (the gene encoding the waaE polypeptide) of which specific antisense molecules SEQ ID NO. 459 and SEQ ID NO. 460 are the elected antisense molecules.

Conclusion

No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
July 26, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER